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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,426	07/02/2001	Kazutoshi Watanabe	P20810	7478

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EXAMINER	
RAO, DEEPAK R	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,426	WATANABE ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *June 12, 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,28,30-33 and 36-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-28, 30-33, 36-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the communication filed on June 12, 2006.

Note: In the previous office action (mailed May 10, 2006) a reference CAPLUS Abstract 84:44112, was inadvertently omitted. The reference is now cited on PTO-892 and a copy is enclosed herewith. Copies of other non-patent documents cited in PTO-892 are not enclosed with this office action because they were submitted previously.

Claims 27-28, 30-33 and 36-42 are pending in this application.

Withdrawn Rejections/Objections:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The following rejections are under new grounds:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-28, 30-33 and 36-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of Formula I or a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for a **solvate** or **hydrate** of a compound of Formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factual Basis:

1. Specification has no working example of solvate of compound of Formula (I); and some of the exemplified compounds within the claimed genus were in contact with solvent. Yet they have not formed solvate as evident form spectral data provided for these compounds.

2. Searching the pertinent art in the related pyrimidinone area did not result in support for such solvates of instant pyrimidinone compounds. Searching the more general area of solvates resulted in pertinent reference West applied below. West clearly shows lack of predictability of the art in the solvate area.

Based on these two facts, a scope of enablement rejection follows using relevant Wands factors. Hence, the burden of establishing the *prime facie* case is met with.

Scope of enablement rejection:

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. **The nature of the invention and the state of the prior art:**

The invention is drawn to compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof. Specification is not adequately enabled as to how to make solvate of compounds of formula (I) Specification has no example of solvate of the instant compounds. Specification on page 18 recites that 'solvates and hydrates of the compounds also fall within the scope of the invention' but there is no enabling disclosure of such hydrates or solvates.

The compound of formula I embrace substituted pyrimidinone compounds substituted with variable groups R^1, R^2, R^3. Careful calculation of the number of compounds embraced in the instant formula (I) shows a large number of compounds. The term "substituted" embraces undefined number of variable groups and thus, the genus embraced by the claims is excessively large and there is no teaching of any solvate of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of solvate formation in general. The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared

with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate. In the instant case of solvate a similar reasoning therefore apply. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to water.

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of solvates in unpredictable. See entire document especially page 18, right column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds".

Joachim Ulrich (Kirk-Othmer Encyclopedia of Chemical Technology) provides that "Pseudopolymorphs are solvates or in the case of water as solvent, hydrates, which means crystals that incorporate solvent molecules into the crystal lattice. Pseudopolymorphs exhibit different crystal forms and/or different densities, solubilities, dissolution rates, colors, hardnesses, etc. Compared with polymorphs, there is an additional degree of freedom (than temperature and pressure), which means a different solvent or even the moisture of the air that might change the stabile region of the pseudopolymorph".

2. **The predictability or lack thereof in the art:**

Hence the solvate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

3. **The amount of direction or guidance present:**

Examples illustrated in the experimental section are limited to making the compounds not

related to solvates. There is no example of solvate of instant compound. Many of the exemplified compounds were shown in the specification that have come in contact with water and/or other solvent but there is showing that these compounds formed solvates. Hence it is clear that merely bringing the compound and water or solvent together does not result in solvate and additional direction or guidance is needed to make them - specification has no such direction or guidance.

4. **The presence or absence of working examples:**

Determining if any particular substrate would form a solvate or hydrate would require synthesis of the substrate and subjecting it to recrystallization with a variety of solvents, temperatures and other parameters. The experimentation is potentially open-ended. The direction concerning the solvates and hydrates is found on page 18, which simply states that 'solvates and hydrates fall within the scope of the invention', however, there is no working example of any hydrate or solvate formed.

The claims are drawn to solvate, yet the numerous examples presented all failed to produce a solvate or even solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "[T]he specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed.

Hence, there should be showing supporting that solvates of these compounds exists and therefore can be made.

5. **The breadth of the claims & the quantity of experimentation needed:**

Specification provides no support, as noted above, for compounds generically embraced in the claim 1 would lead to desired solvate of the compound of formula (I). As noted above, the genus embraces a large number of compounds and hence the claims are extremely broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired solvate of compound of formula (I) embraced in the instant claims in view of the pertinent reference teachings.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 27, 30-32, 35-37, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skulnick et al. (J. Med. Chem. 1985). The reference teaches pyrimidinone compounds having antiviral activity, see the structural formulae in page 1864, Scheme I and the species in Table I, particularly compounds 112-113. The instant claims have the substituent R^1 at the 2-position which is defined to be $-N(R^4)-W-R^5$ wherein R^4 is hydrogen, W can be a bond and R^5 is alkyl e.g., methyl, i.e., the instant compounds have a $-NH-CH_3$ substituent at the 2-position as compared to the $2-NH_2$ of the reference compounds. Therefore, the instantly claimed compounds differ from the reference compounds by a $-CH_2$ group and it is well established that compounds that differ by a $-CH_2$ group are structural homologs. It would have been obvious to one having ordinary skill in the art at the time of the invention to modify the reference compounds to prepare the structural homolog. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds are expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are *prima facie* obvious, absent a showing of unexpected results. *In re Hass*, 60 USPQ 544 (CCPA 1944); *In re Henze*, 85 USPQ 261 (CCPA 1950).

Tertiary versus secondary amines are homologues. Mono-substituted piperazines were found unpatentable over disubstituted piperazines in *Ex Parte Weston & Hamlin* 121 USPQ 428. It was stated "... any chemist is readily aware of the difference between secondary and tertiary amines, including their reactivities, particularly with respect to the possibility of further

substitution for the H in the secondary amine." *Ex parte Bluestone*, 135 USPQ 199, and *In re Doebel*, 179 USPQ 158 further affirm that N-CH_3 is obvious over N-H. *In re Hoeksema*, 154 USPQ 169 in stating that secondary and primary amines are homologues state "...a chemist looking at the formula for another compound which differs so slightly that it is called a homolog generally expects the second compound to have properties similar to the first one."

Applicant's arguments filed on January 17, 2006 based on the Skulnick reference have been fully considered but they were not deemed to be persuasive. Applicant argues that 'the reference is determining the effects of molecular modifications at the 6-position of the disclosed compounds and there is no motivation to modify the primary amine to secondary amine'. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). Reference must be considered under 35 U.S.C. 103, not only for what it expressly teaches but also for what it fairly suggests, in determining obviousness. *In re Burckel*, 201 USPQ 67 (CCPA 1979). The necessary motivation to make the structurally analogous compounds of the reference disclosed compound rises from the expectation that compounds, similar in structure will have similar properties and therefore, the same use, i.e., as antiviral agents.

It is to be noted that rejection under 35 U.S.C. 103 is proper where the subject matter claimed "is not *identically* disclosed or described" in the prior art, and the prior art directs those skilled in the art to the compounds, without any need for picking, choosing, and combining various disclosures. See *In re Shaumann et al.*, 572 F.2d 312, 315, 316, 197 USPQ 5, 8, (CCPA

1978). Further, the reference teaches that the compounds are useful as pharmaceutical agents, which is sufficient to one of ordinary skill to make the claimed compounds because similar properties are normally presumed when compounds are very close in structure. Where the specific compound falls within the ambit of a "very limited number of compounds", the fact that a specific embodiment is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered." *In re Lamberti*, 545 F.2d 747,750, 192 USPQ 278, 280 (CCPA 1976). "The question under 35 U.S.C. 103 is not merely what the reference expressly teaches but what it would have suggested to one of ordinary skill in the art at the time the invention was made."

"Structural relationships provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." See *In re Duel*, 51 F.3d at 1558, 34 USPQ2d at 1214. The closer the physical and chemical similarities between the claimed species or subgenus and any exemplary species or subgenus disclosed in the prior art, the greater the expectation that the claimed subject matter will function in an equivalent manner to the genus. See *In re Dillon*, 919 F.2d at 696, 16 USPQ2d at 1904.

2. Claims 27, 30-33, 35-37, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tani et al., JP 49035631 (see the corresponding CAPLUS Abstract 84:44112). The reference teaches pyrimidinone compounds having antiinflammatory activity, see the compound having RN 54950-14-0 in the enclosed copy of the CAPLUS Abstract. The instant claim 27 recites the substituent R^1 at the 2-position which is defined to be $-N(R^4)-W-R^5$ wherein R^4 is hydrogen, W can be a bond and R^5 is alkyl e.g., methyl, i.e., the instant compounds have a -

NH-CH_3 substituent at the 2-position as compared to the 2-$N(CH_3)_2$ of the reference compound. The instant claim 33 recites a substituent –$N(R^4)$-W-R^5 at the 2-position wherein R^4 can be H or alkyl and R^5 is alkyl selected from ethyl, etc., for example, a substituent of –$N(CH_3)(CH_2CH_3)$ as compared to the –$N(CH_3)_2$ of the reference compound. Therefore, the instantly claimed compounds differ from the reference compounds by a -CH_2 group and it is well established that compounds that differ by a -CH_2 group are structural homologs. It would have been obvious to one having ordinary skill in the art at the time of the invention to modify the reference compounds to prepare the structural homolog. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds are expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are *prima facie* obvious, absent a showing of unexpected results. *In re Hass*, 60 USPQ 544 (CCPA 1944); *In re Henze*, 85 USPQ 261 (CCPA 1950).

Tertiary versus secondary amines are homologues. Mono-substituted piperazines were found unpatentable over disubstituted piperazines in *Ex Parte Weston & Hamlin* 121 USPQ 428. It was stated "... any chemist is readily aware of the difference between secondary and tertiary amines, including their reactivities, particularly with respect to the possibility of further substitution for the H in the secondary amine." *Ex parte Bluestone*, 135 USPQ 199, and *In re Doebel*, 179 USPQ 158 further affirm that N-CH_3 is obvious over N-H. *In re Hoeksema*, 154 USPQ 169 in stating that secondary and primary amines are homologues state "...a chemist looking at the formula for another compound which differs so slightly that it is called a homolog generally expects the second compound to have properties similar to the first one."

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 27-28, 30-33, and 35-41 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2 and 4 of U.S. Patent No. 6,844,335. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed compounds are structural analogs of the reference compounds. The reference teaches and claims pyrimidin-4(3H)-one compounds and the corresponding pharmaceutical composition, see the compounds recited in claim 2, having a methyl group (CH_3) attached to the nitrogen at the 3-position, see e.g., the compound 2-[(phenylmethyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one (col. 38, lines 7-8). The instant claims are drawn to compounds of formula (I) wherein in the 3-position nitrogen has hydrogen (H) attached. Therefore, the instantly claimed compounds differ from the reference compounds by a CH_2

group and it is well established that compounds that differ by a CH_2 group are structural homologs. It would have been obvious to one having ordinary skill in the art at the time of the invention to modify the reference compounds to prepare the structural homolog. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds are expected to possess similar properties.

2. Claims 27-28, 30-33 and 36-42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 7, 16-35 of copending Application No. 11/035,264. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed compounds are structural analogs of the reference compounds. The reference teaches and claims pyrimidin-4(3H)-one compounds and the corresponding pharmaceutical composition, see the compounds recited in claim 1, formula (I) wherein R^4 is defined to be alkyl, e.g., methyl (CH_3). The instant claims are drawn to compounds of formula (I) wherein in the 3-position nitrogen has hydrogen (H) attached. Therefore, the instantly claimed compounds differ from the reference compounds by a CH_2 group and it is well established that compounds that differ by a CH_2 group are structural homologs. It would have been obvious to one having ordinary skill in the art at the time of the invention to modify the reference compounds to prepare the structural homolog. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds are expected to possess similar properties.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Receipt is acknowledged of the Information Disclosure Statement filed on January 31, 2006 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

June 15, 2006